The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

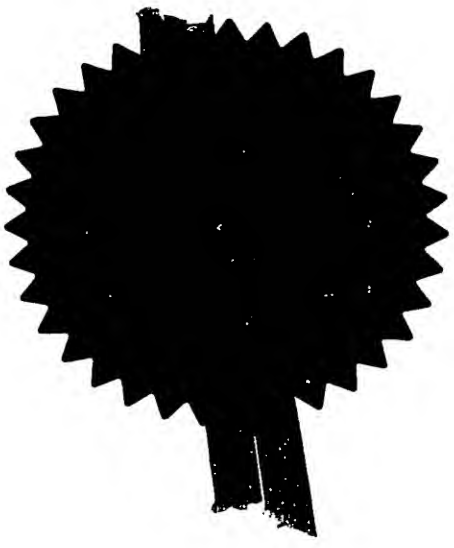
PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed

Dated 13 July 2004

28JUL03 E825525-1 D00245
P01/7700 0.00-0317491.9

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
A
25 JUL 2003
LONDON

The Patent Office

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
South Wales NP10 8QQ

1.	Your reference	4-33256P1	
2.	Patent application number *(The Patent Office will fill in this part)*	0317491.9	25 JUL 2003
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND	
	Patent ADP number *(if you know it)*		
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND	7125487005
4.	Title of invention	Organic compounds	
5.	Name of your agent *(If you have one)*	Bernard Marsh	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham, West Sussex RH12 5AB	
	Patents ADP number *(if you know it)*	07181522002	

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes		

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	32 ✓
Claim(s)	3 ✓
Abstract	
Drawing(s)	

CF

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	**One**
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature — Date

Bernard Cheal — **25th July 2003**

12. Name and daytime telephone number of person to contact in the United Kingdom — **Mrs. S. Schnerr** — **01403 323069**

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *Once you have filled in the form you must remember to sign and date it.*

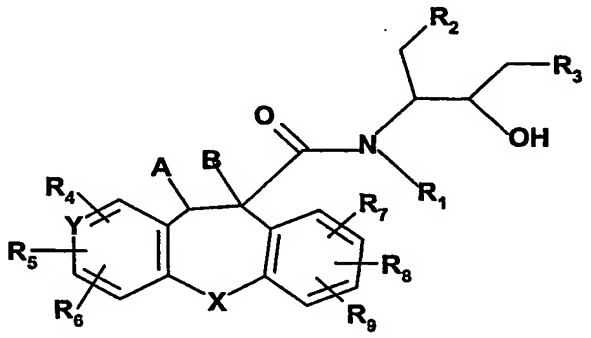
e) *For details of the fee and ways to pay please contact the Patent Office.*

DUPLICATE

Organic Compounds

The present invention relates to novel dibenzo[b,f]oxepine-10-carboxamides, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

More particularly the invention provides compounds of formula I



I

wherein

X is O, NH, N(C_{1-4})alkyl, CO or CHOH,

Y is CH or N,

A and B are each hydrogen or together form a second bond between the carbon atoms to which they are attached,

R_1 is hydrogen or (C_{1-4})alkyl,

R_2 is optionally substituted (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl or heteroaryl,

R_3 is $CH(R_e)CONR_aR_b$ or $(CH_2)_nNR_cR_d$,

n is 0, 1 or 2,

R_a, R_b, R_c and R_d, independently, are hydrogen or optionally substituted (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl, aryl(C_{1-4})alkyl, heteroaryl or heteroaryl(C_{1-4})alkyl or

R_a, R_b, R_c and R_d, together with the nitrogen to which they are attached, form an optionally substituted pyrrolidinyl, piperidino, morpholino or piperazinyl group,

R_e is (C_{1-8})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl(C_{1-4})alkyl, and

R_4, R_5, R_6, R_7, R_8 and R_9, independently, are hydrogen, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})alkyl-SO_2, cyano, nitro or halogen,

in free base or acid addition salt form.

On account of the asymmetrical carbon atoms present in the compounds of formula I and their salts, the compounds may exist in optically active form or in form of mixtures of optical isomers, e.g. in form of racemic mixtures. All optical isomers and their mixtures including the racemic mixtures are part of the present invention.

Halogen denotes fluorine, bromine, chlorine or iodine.

Substituents on above defined non-aromatic groups are selected from hydroxy, halogen, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkoxy, (C_{1-4})alkylsulfanyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyloxy, (C_{1-4})alkylcarbonyl, (C_{1-4})sulfonyl, cyano, oxo, hetero (C_{3-7})cycloalkyl, optionally substituted aryl or heteroaryl.

Substituents on above defined aromatic or heteroaromatic groups are selected from halogen, hydroxy, cyano, nitro, trifluoromethyl, benzyloxy, phenoxy, SO_2NH_2, $NHSO_2$(C_{1-3}) alkyl, carboxy, (C_{1-4})alkyloxycarbonyl, (C_{1-4})alkylcarbamoyl, (C_{1-4})alkylsulfonyl, (C_{1-4}) alkylcarbonyloxy, (C_{1-4})alkylcarbonyl, (C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy(C_{1-4})alkyl, aryl, heteroaryl or optionally substituted amino.

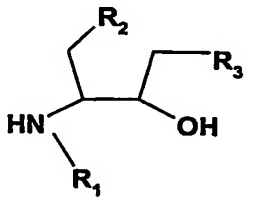
Substitutents on amino groups can be one or two groups selected from (C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{1-4})alkoxycarbonyl, aryl(C_{1-4})alkyloxycarbonyl or heteroaryl(C_{1-4}) alkyloxycarbonyl.

Aryl is an aromatic 6-membered ring optionally mono-, di- or tri-substituted by, independently, hydroxy, cyano, trifluoromethyl, carboxy, (C_{1-4})alkyloxycarbonyl, (C_{1-4})alkylcarbamoyl, (C_{1-4})alkylsulfonyl, (C_{1-4}) alkylcarbonyloxy, (C_{1-4})alkylcarbonylamino, (C_{1-4})alkylcarbonyl, (C_{1-4})alkyl, (C_{1-4})alkoxy or hydroxy(C_{1-4})alkyl. It can also be fused with a cycloalkyl or additional aromatic or heteroaromatic ring (e.g. to form a naphthyl, quinolinyl or indolyl group).

Heteroaryl is an aromatic 5- or 6- membered ring in which 1, 2 or 3 atoms are heteroatoms independently selected from O, N and S. Heteroaryl is for example 1-methyl-1H-pyrrol-2-yl or 1H-imidazol-2-yl. It can also be fused with a cycloalkyl or additional aromatic or heteroaromatic ring (e.g. to form a quinolinyl, or indolyl group).

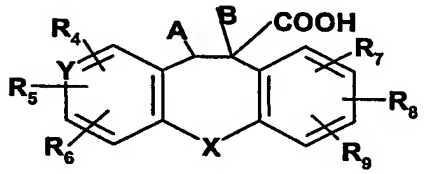
Any alkyl or alkoxy group is straight or branched.

In a further aspect, the invention provides a process for the production of the compounds of formula I and their salts, comprising the steps of acylating a compound of formula II



II

wherein R_1, R_2 and R_3 are as defined above, with an acid of formula III



III

wherein X, Y, A, B, R_4, R_5, R_6, R_7, R_8 and R_9 are as defined above, or an activated form thereof, and recovering the so obtained compound of formula I in free base or acid addition salt form.

The reaction can be effected according to conventional methods, for example as described in the examples.

The compounds of formula I can also be produced by further conventional processes, e.g. as described in the examples.

The starting materials of formulae II and III are known or may be prepared according to conventional procedures starting from known compounds, for example as described in the examples.

Working-up the reaction mixtures and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Acid addition salts may be produced from the free bases in known manner, and vice-versa.

Compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as pharmaceuticals.

The agents of the invention are inhibitors of aspartic proteases and can be used for the treatment of disorders involving processing by such enzymes. Particularly they inhibit beta-secretase and as such inhibit the generation of beta-amyloid and the subsequent aggregation into oligomers and fibrils.

Test 1 Inhibition of human BACE

Recombinant BACE (extracellular domain, expressed in baculovirus and purified using standard methods) at 6 nM concentration is incubated with test compound at various concentrations for 1 hour at room temperature in 100 mM acetate buffer, pH 4.5, containing 0.1 % CHAPS. Synthetic peptide substrate Mca-Ser-Glu-Val-Asn-Leu-Asp-Ala-Glu-Phe-Lys(DNP) is added to a final concentration of 3 µM and increase in fluorescence is recorded at excitation of 325 nm and emission at 400 nm in a microplate spectro-fluorimeter for 20 minutes in 1-minute intervals. IC_{50} values are calculated from percentage of inhibition of BACE-activity as a function of test compound concentration.

Test 2 Inhibition of human BACE-2

Recombinant BACE-2 (extracellular domain, expressed in baculovirus and purified using standard methods) at 2.5 nM concentrations incubated with test compound at various concentrations for 1 hour at room temperature in 100 mM acetate buffer, pH 4.5, containing 0.1 % CHAPS. Synthetic peptide substrate Mca-Ser-Glu-Val-Asn-Leu-Asp-Ala-Glu-Phe-Lys(DNP) is added to a final concentration of 3 µM and increase in fluorescence is recorded at excitation of 325 nm and emission at 400 nm in a microplate spectro-fluorimeter for 20 minutes in 1-minute intervals. IC_{50} values are calculated from percentage of inhibition of BACE-2-activity as a function of test compound concentration.

Test 3 Inhibition of human Cathepsin D

Recombinant cathepsin D (expressed as procathepsin D in baculovirus, purified using standard methods and activated by incubation in sodium formate buffer pH 3.7) is incubated with test compound at various concentrations for 1 hour at room temperature in 100 mM sodium formate buffer, pH 3.1. Synthetic peptide substrate Mca-Gly-Lys-Pro-Ile-Leu-Phe-Phe-Arg-Leu-Lys(DNP)-D-Arg-NH_2 is added to a final concentration of 2 µM and increase in fluorescence is recorded at excitation of 325 nm and emission at 400 nm in a microplate spectro-fluorimeter for 20 minutes in 1-minute intervals. IC_{50} values are calculated from percentage of inhibition of cathepsin D-activity as a function of test compound concentration.

Test 4 Inhibition of cellular release of amyloid peptide 1-40

Chinese hamster ovary cells are transfected with the gene for amyloid precursor protein. Cells are plated at a density of 8000 cells/well in a 96- well microtiter plate and cultivated for 24 hours in DMEM cell culture medium containing 10 % FCS. Test compound is added to the cells at various concentrations, and cells are cultivated for 24 hours in presence of test compound. Supernatants are collected, and concentration of amyloid peptide 1-40 is determined using sandwich ELISA. Potency of the compound is calculated from the percentage of inhibition of amyloid peptide release as a function of test compound concentration.

In at least one of the above-indicated tests, the agents of the invention show activity at concentrations below 20 µM.

The agents of the invention are therefore useful e.g. for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation and/or aggregation such as neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral haemorrhage with amyloidosis.

Some of the agents of the invention also inhibit BACE2 (beta-site APP-cleaving enzyme 2) or Cathepsin D, close homologues of the pepsin-type aspartyl proteases. Due to the correlation of BACE2 and CathD expression with a more tumorigenic and metastatic potential of tumor cells, such inhibitors are useful for the suppression of the metastasis process associated with tumor cells.

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.1 to about 100, preferably from about 1 to about 50 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 10 to about 2000, preferably from about 10 to about 200 mg of an agent of the invention conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

In accordance with the foregoing, the present invention also provides an agent of the invention, for use as a pharmaceutical, e.g. for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 1 to about 1000, preferably from about 1 to about 500 mg of an agent of the invention.

The agents of the invention can be administered alone or in combination with other pharmaceutical agents effective, in the treatment of conditions mentioned above.

The pharmaceutical combination may be in form of a unit dosage form, whereby each unit dosage will comprise a predetermined amount of the two components, in admixture with suitable pharmaceutical carriers or diluents. Alternatively, the combination may be in form of a package containing the two components separately, e.g. a pack or dispenser-device adapted for the concomitant or separate administration of the two active agents, wherein these agents are separately arranged.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of any neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

In still a further aspect the present invention provides a method for the treatment of any neurological and vascular disorders related to beta-amyloid generation and/or aggregation, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following examples illustrate the invention.

Abbreviations:

BOC	tert-butoxycarbonyl
BOP	benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate
DCM	dichloromethane
DMPU	N, N'-dimethylpropyleneurea
EDCI	1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride
EtOAc	ethylacetate
h	hours
HCl	hydrochloric acid
HOBt	hydroxybenzotriazole
HPLC	high pressure liquid chromatography
LAH	lithium aluminum hydride
min	minutes
Mp	melting point
MS	mass spectroscopy
Rf	retention factor (TLC)
rt	room temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Example 1: 10,11-Dihydro-dibenzo[b,f]oxepine-10-carboxylic acid [(1S*,2S*,4R*)-4-butylcarbamoyl-2-hydroxy-1-(3-hydroxy-benzyl)-pentyl]-amide

Dibenzo[b,f]oxepine-10-carboxylic acid [(1S*,2S*,4R*)-1-(3-benzyloxy-benzyl)-4-butylcarbamoyl-2-hydroxy-pentyl]-amide 200mg, 0.3mmol) is hydrogenated (5 atm H_2) at rt with 10% Pd/C (Engelhard 4505, 40mg) during 15h. The catalyst is filtered off and the solvent evaporated. The residue is chromatographed on silica (Flashmaster, DCM to DCM/methanol 85/15) followed by recrystallization from DCM/ether/hexane to give the racemic 1/1-mixture of the two diastereoisomers as white solid (140mg).

MS (LC/MS): 553 [M+Na]
1H-NMR (400MHz, $C_2D_2Cl_4$): 7.45-7.0 (m. 9H), 6.77-6.60 (m, 3H), 5.7-5.52 (m, 2H), 5.32 (br s, 1H), 4.1-3.9 (m, 2H), 3.6-3.35 (m, 3H), 3.3-3.15 (m, 2H), 3.0-2.5 (m, 2H), 2.55-2.45 (m, 1H), 1.65-1.25 (m, 5H), 1.14 (t, 3H), 1.0-0.95 (m, 3H).

The starting materials can be prepared as described hereafter:

a) [1-Benzenesulfonyl-2-(3-benzyloxy-phenyl)-ethyl]-carbamic acid tert-butyl ester

A suspension of (3-Benzyloxy-phenyl)-acetaldehyde (20.6g, 91mmol), tert-butylcarbamate (10.7g, 91mmol, 1eq), sodium benzenesulfinate (18.3g, 109mmol, 1.2eq) and formic acid (5.2ml, 137mmol, 1.5eq) in 155 ml acetonitrile is stirred at 80°C for 4 h. After cooling to rt the mixture is taken up in EtOAc. The solution is washed with bicarbonate and brine, dried over magnesium sulfate and evaporated. The residue (37.3g) is used for the next step without further purification.

MS (LC/MS): 490 [M+Na]

b) [(S*)-2-(3-Benzyloxy-phenyl)-1-((S*)-5-oxo-2,5-dihydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester

5H-Furan-2-one (11.2ml, 160mmol, 2eq) in THF (60ml) is added slowly to a solution of lithium diisopropylamide (80ml commercial 2M solution in THF/heptane/ethylbenzene, 160mmol, 2eq) in THF (180ml) at -78°C. The mixture is stirred for another 20min at -78°C

before [1-Benzenesulfonyl-2-(4-benzyloxy-phenyl)-ethyl]-carbamic acid tert-butyl ester (37.3g, 80mmol) in THF (220ml) is added at the same temperature. After stirring for another 45 min at -78°C aqueous bicarbonate solution is added and the reaction mixture is taken up into EtOAc. The organic layer is washed with bicarbonate and brine and dried over magnesium sulfate. Evaporation of the solvent gives a residue that is purified by chromatography on silica using hexan/EtOAc 9/1 to 7/3. The product is recrystallized from ether/hexane to give the product as white crystals (11.1g)

MS (LC/MS): 432 [M+Na]
1H-NMR (400MHz, $CDCl_3$): 7.45-7.2 (m, 7H), 6.9-6.85 (m, 3H), 6.06 (d, 1H), 5.07 (s, 2H), 4.90 (d, 1H), 4.50 (d, 1H), 4.20 (q, 1H), 3.01 (dd, 1H), 2.91 (dd, 1H), 1.38 (s, 9H).

c) [(S*)-2-(3-Benzyloxy-phenyl)-1-((S*)-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester

[(S*)-2-(4-Benzyloxy-phenyl)-1-((S*)-5-oxo-2,5-dihydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester (11.1g, 27mmol) is hydrogenated (1atm H_2) at rt in THF (550ml) with Pt/C as catalyst (5% Engelhard 4709, 2.3g) during 1h. The catalyst is filtered off and the filtrate is evaporated. Purification by chromatography on silica (Flashmaster, hexane to hexane/EtOAc 55/45 over 40min) gives the product as yellowish oil (10.4g).

MS (LC/MS): 434 [M+Na]
1H-NMR (400MHz, $CDCl_3$): 7.45-7.2 (m, 6H), 6.9-6.8 (m, 3H), 5.06 (s, 2H), 4.61 (d, 1H), 4.44 (t, 1H), 4.00 (q, 1H), 2.95 (dd, 1H), 2.85 (dd, 1H), 2.6-2.45 (m, 2H), 2.15-2.1 (m, 2H), 1.42 (s, 9H).

d) [(S*)-2-(3-Benzyloxy-phenyl)-1-((2S*,4R*)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester

To a solution of [(S*)-2-(4-Benzyloxy-phenyl)-1-((S*)-5-oxo-2,5-dihydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester (11.4g, 27.7mmol) in THF (35ml) and DMPU (5ml, 42mmol, 1.5eq) at -78°C is added dropwise lithium-bis-(trimethylsilyl)-amide (55ml 1M solution in THF, 55mmol, 2eq). After stirring at -78°C for another 45 min methyliodide is added dropwise and the mixture is stirred another 3h at -78°C. Propionic acid (10.3 ml, 138mmol,

5eq) is added followed by water (10ml). After warming up to 0°C a 10% solution of citric acid (72ml) is added. The reaction mixture is extracted with EtOAc. The organic layer is washed with bicarbonate, 0.1N sodium sulfite and brine, dried over magnesium sulfate and evaporated. Purification by chromatography on silica (hexane/EtOAc 9/1 to 4/1) followed by recrystallization from ether/hexane gives white crystals (8.14g).

MS (LC/MS): 448 [M+Na]
1H-NMR (400MHz, $CDCl_3$): 7.45-7.2 (m, 6H), 6.9-6.8 (m, 3H), 5.05 (s, 2H), 4.53 (d, 1H), 4.45 (t, 1H), 4.00 (q, 1H), 2.93-2.85 (m, 2H), 2.74-2.68 (m, 1H), 2.41-2.34 (m, 1H), 1.89-1.82 (m, 1H), 1.41 (s, 9H), 1.26 (d, 3H).

e) [(1S*,2S*,4R*)-1-(3-Benzyloxy-benzyl)-4-butylcarbamoyl-2-hydroxy-pentyl]-carbamic acid tert-butyl ester

[(S*)-2-(3-Benzyloxy-phenyl)-1-((2S*,4R*)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester (4.0g, 9.4mmol) is dissolved in butylamine (200ml) and stirred for 18 h in an heating bath of 90°C. The butylamine is evaporated and the residue is recrystallized from DCM/ether/hexane to give white crystals (4.42g).

MS (LC/MS): 521 [M+Na]
1H-NMR (400MHz, CDCl3): 7.45-7.15 (m, 6H), 6.9-6.8 (m, 3H), 5.91 (s, 1H), 5.04 (s, 2H), 4.89 (d, 1H), 3.7-3.6 (m, 2H), 3.3-3.1 (m, 2H), 2.9-2.85 (m, 2H), 2.6-2.5 (m, 1H), 1.75-1.6 (m, 2H), 1.5-1.25 (m, 4H), 1.41 (s, 9H), 1.12 (d, 3H), 0.92 (t, 3H).

f) (1S*,2S*,4R*)-1-(3-Benzyloxy-benzyl)-4-butylcarbamoyl-2-hydroxy-pentyl-ammonium chloride

[(1S*,2S*,4R*)-1-(3-Benzyloxy-benzyl)-4-butylcarbamoyl-2-hydroxy-pentyl]-carbamic acid tert-butyl ester (660mg, 1.3mmol) is dissolved in 4M HCl in dioxane (14ml) and stirred at rt for 75 min. Evaporation of the solvent and washing the residue with diethyl ether gives a white foam (535mg).

MS (LC/MS): 421 [M+Na]

1H-NMR (400MHz, $CDCl_3$): 7.45-7.30 (m, 6H), 6.89-6.75 (m, 3H), 6.03 (br s, 1H), 5.05 (s, 2H), 3.41-3.38 (m, 1H), 3.30-3.16 (m, 2H), 2.95-2.85 (m, 2H), 2.68-2.50 (m, 2H), 1.89 (dt, 1H), 1.53-1.44 (m, 3H), 1.40-1.27 (m, 2H), 1.18 (d, 3H), 0.92 (t, 3H).

g) Dibenzo[b,f]oxepine-10-carboxylic acid [(1S*,2S*,4R*)-1-(3-benzyloxy-benzyl)-4-butylcarbamoyl-2-hydroxy-pentyl]-amide

(1S*,2S*,4R*)-1-(3-Benzyloxy-benzyl)-4-butylcarbamoyl-2-hydroxy-pentyl-ammonium chloride (210mg, 0.48mmol), Dibenzo[b,f]oxepine-10-carboxylic acid (138mg, 0.58mmol, 1.2eq), EDCI (139mg, 0.72mmol, 1.5eq), HOBt (78mg, 0.58mmol, 1.2eq) and triethylamine (0.20ml, 1.4mmol, 3eq) are dissolved in DCM (12ml) and strirred at rt for 3 days. EtOAc is added. After washing with 0.5 N HCl, brine, bicarbonate and brine again, drying over magnesium sulfate, the solvent is evaporated and the residue recrystallized from DCM/ether/hexane with a drop of methanol to give a white solid (240mg).

MS (LC/MS): 641 [M+Na]
1H-NMR (400MHz, $C_2D_2Cl_4$, 90°C): 7.5-7.1 (m, 15H), 7.0-6.9 (m, 3H), 6.18 (d, 1H), 5.7 (s, 1H), 5.14 (s, 2H), 4.38 (q, 1H), 3.92-3.83 (m, 2H), 3.33-3.23 (m, 2H), 3.12-3.03 (m, 2H), 2.65- 2.6 (m, 1H), 1.87-1.75 (m, 2H), 1.57-1.50 (m, 2H), 1.45-1.35 (m, 2H), 1.25 (d, 3H), 0.97 (t, 3H).

Example 2: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S*,2S*,4R*)-4-butylcarbamoyl-2-hydroxy-1-(3-hydroxy-benzyl)-pentyl]-amide

[(1S*,2S*,4R*)-4-Butylcarbamoyl-2-hydroxy-1-(3-hydroxy-benzyl)-pentyl]-carbamic acid tert-butyl ester (175mg) is dissolved in 4M HCl in dioxane and stirred at rt for 75min. The solvent is evaporated and the residue washed with ether to give a foam. The foam is redissolved in DCM and added to the mixture of bicarbonate (4.25ml, 10% solution in water) and the DCM solution of dibenzo[b,f]oxepine-10-carboxylic acid chloride [prepared in situ by stirring dibenzo[b,f]oxepine-10-carboxylic acid (103mg, 0.43mmol, 1.1eq), oxalyl chloride (0.037ml, 0.43mmol, 1.1eq) with one drop of DMF in 4ml DCM for 30min]. The two layer system is stirred vigorously at rt for 2h. EtOAc is added and the organic layer is washed with 0.5N HCl, brine, bicarbonate and brine again. Drying over magnesium sulfate and evaporation of the

solvent gives residue that is purified by chromatography on silica (Flashmaster, DCM to DCM/methanol 9/1). Recrystallization from DCM/ether/hexane gives 140mg white solid.

MS (LC/MS): 551 [M+Na]
1H-NMR (400MHz, $C_2D_2Cl_4$): 74-7.1 (m, 10H), 7.07 (t, 1H), 6.85-6.80 (m, 4H), 6.45 (d, 1H), 4.72 (s, 1H), 4. 32 (q, 1H), 3.82-3.78 (m, 1H), 3.3-3.15 (m, 2H), 3.03-2.97 (m, 2H), 2.65-2.58 (m, 1H), 1.9-1.6 (m, 2H), 1.5-1.4 (m, 2H), 1.438-1.28 (m, 2H), 1.20 (d, 3H), 0.90 (t, 3H).

The starting materials can be prepared as described hereafter:

a) [(1S*,2S*,4R*)-4-Butylcarbamoyl-2-hydroxy-1-(3-hydroxy-benzyl)-pentyl]-carbamic acid tert-butyl ester

[(1S*,2S*,4R*)-1-(3-Benzyloxy-benzyl)-4-butylcarbamoyl-2-hydroxy-pentyl]-carbamic acid tert-butyl ester (240mg, 0.48mmol) is hydrogenated (5atm H_2) at rt with 10% Pd/C (Engelhard 4505, 60mg) for 2h. The catalyst is filtered off and after evaporation the residue is purified by chromatography on silica (Flashmaster, DCM to DCM / methanol 85/15) to give a white foam (184mg).

MS (LC/MS): 431 [M+Na]
1H-NMR (400MHz, $CDCl_3$): 7.44 (s, 1H), 7.11 (t, 1H), 6.74-6.7 (m, 2H), 6.11 (t, 1H), 5.07 (d, 1H), 4.25 (br s, 1H), 3.72-3.58 (m, 2H), 3.3-3.1 (m, 2H), 2.9-2.75 (m, 2H), 2.60-2.50 (m, 1H), 1.75-1.60 (m, 2H), 1.45-1.25 (m, 4H), 1.40 (s, 9H), 1.11 (d, 3H), 0.90 (t, 3H).

Example 3: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-4-butylcarbamoyl-2-hydroxy-1-(4-hydroxy-benzyl)-pentyl]-amide

The title compound is obtained from (S)-2-(4-Benzyloxy-phenyl)-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester following a similar procedure as for dibenzo[b,f]oxepine-10-carboxylic acid [(1S*,2S*,4R*)-4-butylcarbamoyl-2-hydroxy-1-(3-hydroxy-benzyl)-pentyl]-amide.

MS (LC/MS): 551 [M+Na]

1H-NMR (400MHz, $CDCl_3$): 7.3-7.0 (m, 12H), 6.94 (t, 1H), 6.83-6.74 (m, 2H), 6.66 (d, 1H), 4.22 (q, 1H), 3.83-3.76 (m, 1H), 3.3-3.15 (m, 2H), 3.0-2.9 (m, 2H), 2.75-2.65 (m, 1H), 1.75-1.6 (m, 2H), 1.50-1.43 (m, 2H), 1.35-1.25 (m, 3H), 1.17 (d, 3H), 0.88 (t, 3H).

The starting materials can be prepared as described hereafter:

[(S)-2-(4-Benzyloxy-phenyl)-1-((2S,4R)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester

[(S)-2-(4-Benzyloxy-phenyl)-1-((S)-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester (2.9g, 7.04 mmol) is dissolved in THF (10ml) and DMPU (1.34ml, 10.6mmol, 1.5 eq). A 1 M solution of lithium hexamethyldisilazide in THF (14.1 ml, 14.1 mmol, 2eq) is added at -78 °C over 40 min and the mixture is stirred for another 20 min. Methyliodide (0.88ml, 14.1mmol, 2eq) is added dropwise and the mixture is stirred for another 3h at -78°C before adding propionic acid (2.69ml, 36mmol, 5eq) and water. After warming up to rt the mixture is poured on 10% citric acid (50ml) and extracted with EtOAc. The organic layer is washed with bicarbonate and brine, dried over magnesium sulfate and evaporated. The crude product is purified by chromatography on silica (hexane/EtOAc 8/2 to 7/3) followed by recrystallization from hexane/DCM to give 2.2g white solid.

MS (LC/MS): 448 [M+Na]
1H-NMR (400MHz, $CDCl_3$): 7.45-7.28 (m, 5H), 7.13 (d, 2H), 6.81 (d, 2H), 5.05 (s, 2H), 4.55 (d, 1H), 4.48 (dd, 1H), 3.95 (dd, 1H), 2.90-2.80 (m, 2H), 2.78-65 (m, 1H), 2.43-2.33 (m, 1H), 1.90-1.80 (m, 1H), 1.40 (s, 9H), 1.27 (t, 3H).

Example 4: 7-Chloro-dibenzo[b,f]oxepine-10-carboxylic acid ((1S,2S,4R)-4-butylcarbamoyl-2-hydroxy-1-isobutyl-pentyl)-amide

((1S,2S,4R)-4-Butylcarbamoyl-2-hydroxy-1-isobutyl-pentyl)-carbamic acid tert-butyl ester (66mg, 0.18mmol) are dissolved in 4N HCl in dioxane (3ml). After stirring for 1h at rt the solvent is evaporated and the residue dried in vacuum. The residue is dissolved in DCM (3ml) and 7-Chloro-dibenzo[b,f]oxepine-10-carboxylic acid (60mg, 0.22mmol, 1.2eq), HOBT (30mg, 0.22mmol, 1.2 eq), EDCI (53mg, 0.28mmol, 1.5eq) and triethylamine (0.077ml, 0.55mmol, 3eq) are added. The mixture is stirred over night at rt. The reaction mixture is

diluted with DCM and washed with water, bicarbonate and brine. The organic layer is dried over magnesium sulfate and the solvent is evaporated. Purification on silica (Flashmaster, DCM/methanol 100 % -> 90 %) and crystallization from DCM/hexane gives the products as white crystals (50mg).

MS (LC/MS): 535/537 [M+Na]
1H-NMR (400MHz, CDCl3): 7.49 (s, 1H), 7.38-7.26 (m, 4H), 7.21-7.16 (m, 3H), 6.10 (d, 1H), 5.84 (t, 1H), 4.30 (d, 1H), 4.2-4.1 (m, 1H), 3.82-3.74 (m, 1H), 3.24 (q, 2H), 2.66-2.58 (m, 1H), 1.75 (t, 2H), 1.72-1.59 (m, 2H), 1.51-1.26 (m, 5H), 1.25 (d, 3H), 1.00 (d, 3H), 0.97 (d, 3H), 0.89 (t, 3H).

The following compounds are obtained by a similar procedure:

Example 5: Dibenzo[b,f]oxepine-10-carboxylic acid ((1S,2S,4R)-4-butylcarbamoyl-2-hydroxy-1-isobutyl-pentyl)-amide

MS (LC/MS): 501 [M+Na]
1H-NMR (400MHz, $CDCl_3$): 7.56 (s, 1H), 7.39-7.14 (m, 8H), 6.10 (d, 1H), 5.86 (t, 1H), 4.2.4.1 (m, 1H), 4.11 (d, 1H), 3.8-3.7 (m, 1H), 3.24 (q, 2H), 2.65-2.58 (m, 1H), 1.78-1.6 (m, 4H), 1.51-1.25 (m, 5H), 1.24 (d, 3H), 1.01 (d, 3H), 0.97 (d, 3H), 0.89 (t, 3H).

Example 6: 7-Bromo-dibenzo[b,f]oxepine-10-carboxylic acid ((1S,2S,4R)-4-butylcarbamoyl-2-hydroxy-1-isobutyl-pentyl)-amide

MS (LC/MS): 581/583 [M+Na]
1H-NMR (400MHz, $CDCl_3$): 7.51 (s, 1H), 7.44 (s, 1H), 7.39-7.16 (m, 6H), 6.10 (d, 1H), 5.88 (br s, 1H), 4.17-4.11 (m, 1H), 3.78 (t, 1H), 3.24 (q, 2H), 2.67-2.59 (m, 1H), 1.85 (br s, 1H), 1.77-1.6 (m, 4H), 1.51-1.2 (m, 5H), 1.25 (d, 3H), 1.10 (d, 3H), 0.97 (d, 3H), 0.90 (t, 3H).

Example 7: 1-Chloro-dibenzo[b,f]oxepine-10-carboxylic acid ((1S,2S,4R)-4-butylcarbamoyl-2-hydroxy-1-isobutyl-pentyl)-amide

MS (LC/MS): 535/537 [M+Na]

1H-NMR (400MHz, $CDCl_3$): 7.82 (s, 1H), 7.42-7.37 (m, 2H), 7.29-7.19 (m, 4H), 7.15 (d, 1H), 6.12 (d, 1H), 5.94 (br s, 1H), 4.18-4.12 (m, 1H), 3.78 (t, 1H), 3.27-3.21 (m, 2H), 2.64 (q, 1H), 1.8-1.6 (m, 5H), 1.52-1.2 (m, 5H), 1.25 (d, 3H), 1.00 (d, 3H), 0.97 (d, 3H), 0.89 (t, 3H).

Example 8: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-4-butylcarbamoyl-2-hydroxy-pentyl]-amide

This product is prepared from [(S*)-2-(phenyl)-1-((2S*,4R*)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester according to a procedure similar to steps 1f, 1g and 1e of Example 1.

Mp: 188 - 191 °C
MS (LC/MS): 535 [M+Na]
1H-NMR (400MHz, $CDCl_3$): 7.40 (s, 1H), 7.38-7.10 (m, 13H), 6.95 (t, 1H), 6.73 (d, 1H), 4.38 (ddd, 1H), 3.82 (td, 1H), 3.21 (m, 1H), 3.08 (d, 2H), 3.0 (qd, 1H), 2.75-2.70 (m, 1H), 1.80-1.70 (m, 2H), 1.50-1.40 (m, 2H), 1.40 -1.22 (m, 2H), 1.20 (d, 3H), 0.93 (t, 3H).

The following compounds are obtained by a similar procedure:

Example 9: 7-Chloro-dibenzo[b,f]oxepine-10-carboxylic acid (1-benzyl-4-butylcarbamoyl-2-hydroxy-pentyl)-amide

MS (EI+): 547 [M+H]
Mp: 153-155 °C

Example 10: 5H-Dibenzo[b,f]azepine-10-carboxylic acid (1-benzyl-4-butylcarbamoyl-2-hydroxy-pentyl)-amide

MS (EI+): 512 [M+H]
1H-NMR (400 MHz, CDCl3): delta = 7.30-7.0 (m, 7H); 6.90, 6.75 (2t, 2H); 6.68, 6.64, 6.52 (3d, 3H); 6.20 (m, 2H); 4.34 (m, 1H); 3.72 (br s, 1H); 3.18 (m, CH2); 2.97 (d, CH2); 2.55 (m, 1H); 2.02 (br s, NH); 1.64, 1.40, 1.30 (3m, 3CH2); 1.11 (d, CH3); 0.85 (t, CH3).

Example 11: 5-Oxo-5H-dibenzo[a,d]cycloheptene-10-carboxylic acid (1-benzyl-4-butylcarbamoyl-2-hydroxy-pentyl)-amide.

MS (EI+): 525 [M+H]
Mp: 229-230 °C

Example 12: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-2-hydroxy-4-(2-methoxy-ethylcarbamoyl)-pentyl]-amide

Rf: (DCM/methanol = 95/5): 0.48
MS (LC/MS): 537 [M+Na]

Example 13: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-4-(3,3-dimethyl-butylcarbamoyl)-2-hydroxy-pentyl]-amide

Rf: (DCM/methanol = 95/5): 0.51
MS (LC/MS): 563 [M+Na]

Example 14: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-4-(2,2-dimethyl-propylcarbamoyl)-2-hydroxy-pentyl]-amide

Mp: 178-180 °C
MS (LC/MS): 549 [M+Na]

Example 15: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-(4-amino-benzyl)-4-butylcarbamoyl-2-hydroxy-pentyl]-amide

(4-{(2S,3S 5R)-5-Butylcarbamoyl-2-[(dibenzo[b,f]oxepine-10-carbonyl)-amino]-3-hydroxy-hexyl}-phenyl)-carbamic acid benzyl ester (50 mg, 0.076 mmol) is hydrogenated at 1 atm H_2 for 20 h in ethanol (2 ml) at 22 °C in the presence of Pd/C (10 %, 15 mg). The solution is filtered through Celite and the solvent evaporated. The residue is dissolved in DCM (5 ml) and washed with aqueous saturated $NaHCO_3$ (2 x 5 ml). The organic layer is dried over sodium sulfate and the solvent evaporated. Flash-chomatography (silica gel, 2 % ethylamine in EtOAc) affords the desired product (15 mg, 0.028 mmol, 38 %) as a colorless wax.

MS (LC/MS): 550 [M+Na]
1H-NMR (400MHz, d6-DMSO): 8.15 – 6.50 (m, 15H), 4.80 (s, 2H), 4.15-3.80 (m, 2H), 3.21-2.70 (m, 6H), 1.80-1.50 (m, 2H), 1.42 -1.18 (m, 4H), 1.05 (d, 3H), 0.91 (t, 3H).

The starting material can be prepared as described hereafter:

(4-{(2S,3S 5R)-5-Butylcarbamoyl-2-[(dibenzo[b,f]oxepine-10-carbonyl)-amino]-3-hydroxy-hexyl}-phenyl)-carbamic acid benzyl ester

This compound is obtained from [4-(2-Oxo-ethyl)-phenyl]-carbamic acid benzyl ester according to the procedure described in steps a-d of Example 1 and Example 8.

Example 16: Dibenzo[b,f]oxepine-10-carboxylic acid [4-butylcarbamoyl-1-(3,5-difluoro-benzyl)-2-hydroxy-pentyl]-amide

Dibenzo[b,f]oxepine-10-carboxylic acid [2-(3,5-difluoro-phenyl)-1-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-amide (50 mg, 0.105 mmol) is dissolved in 2 ml butylamine and stirred for 16 h. The solution is concentrated in vacuo and the residual solid recrystallized from EtOAc / hexane. Yield 27 mg (48%).

Mp: 174-176 °C
MS (LC/MS): 571 [M+Na]

The starting materials can be prepared as described hereafter:

Dibenzo[b,f]oxepine-10-carboxylic acid [2-(3,5-difluoro-phenyl)-1-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-amide

This compound is obtained from (3,5-difluoro-phenyl)-acetaldehyde according to the procedure described in steps a-d of Example 1 and Example 8.

Example 17: Dibenzo[b,f]oxepine-10-carboxylic acid [4-butylcarbamoyl-1-(3-fluoro-benzyl)-2-hydroxy-pentyl]-amide

Dibenzo[b,f]oxepine-10-carboxylic acid [2-(3-fluoro-phenyl)-1-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-amide (50 mg) is dissolved in 2 ml butylamine and stirred for 16 h. The solution was concentrated in vacuo and the residual solid was recrystallised from EtOAc / hexane. Yield 25 mg (48%).

Mp: 204-207 °C
MS (LC/MS): 553 [M+Na]

The starting materials can be prepared as described hereafter:

Dibenzo[b,f]oxepine-10-carboxylic acid [2-(3-fluoro-phenyl)-1-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-amide

This compound is obtained from (3-fluoro-phenyl)-acetaldehyde according to the procedure described in steps a-d of Example 1 and Example 8.

The following compounds are obtained similarly to Example 8, except for the last step of lactone opening which is effected according to the following general procedure:

A solution of 3-propenyl-2-vinyl-benzo[b]oxepine-4-carboxylic acid [1S-(4R-methyl-5-oxo-tetrahydro-furan-2-yl)-2S-phenyl-ethyl]-amide (0.1mmol) and the aliphatic amine (10 eq, 1 mmol) in 1-methyl-2-pyrrolidon (2 ml) is stirred for 18 h at 110°C. The resulting mixture is cooled to 25 °C, diluted with EtOAc (5 ml) and extracted with 0.1 N HCl (2 x 3 ml) and aqueous $NaHCO_3$ (2 x 3 ml). The organic layer is dried over sodium sulfate and the solvent evaporated. Flash-chomatography (silica gel, hexane/EtOAc) affords the desired product.

Example 18: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-2-hydroxy-4-(4-hydroxy-cyclohexylcarbamoyl)-pentyl]-amide

Mp: 213-217 °C
MS (LC/MS): 577 [M+Na]

Example 19: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-(1-benzyl-2-hydroxy-4-benzylcarbamoyl-pentyl)]-amide

Mp: 204 - 206 °C
MS (LC/MS): 569 [M+Na]

Example 20: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-{1-benzyl-2-hydroxy-4-[(pyridin-2-ylmethyl)-carbamoyl]-pentyl}]-amide

Mp: 194 - 197 °C
MS (LC/MS): 570 [M+Na]

Example 21: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-2-hydroxy-4-(tetrahydro-pyran-4-ylcarbamoyl)-pentyl]-amide

Mp: 251 - 256 °C
MS (LC/MS): 563 [M+Na]

Example 22: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-2-hydroxy-4-(1-methyl-piperidin-4-ylcarbamoyl)-pentyl]-amide

Mp: 206 - 211 °C
MS (LC/MS): 576 [M+Na]

Example 23: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-4-(bicyclo[2.2.1]hept-2-ylcarbamoyl)-2-hydroxy-pentyl]-amide

Rf: (DCM/methanol = 95/5): 0.23
MS (LC/MS): 573 [M+Na]

Example 24: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-4-(cyclobutylmethyl-carbamoyl)-2-hydroxy-pentyl]-amide

Rf: (DCM/methanol = 95/5): 0.25
MS (LC/MS): 547 [M+Na]

The following compounds are obtained similarly to Example 8, except for the last step of lactone opening which is effected according to the following general procedure:

Trimethylaluminum (2 M solution in hexane, 2 mmol, 20 eq) is added over 20 min to a solution of the aromatic amine (1 mmol, 10 eq) in DCM (2 ml). After stirring the resulting mixture for 45 min at 25 °C, a solution of 3-propenyl-2-vinyl-benzo[b]oxepine-4-carboxylic acid [1S-(4R-methyl-5-oxo-tetrahydro-furan-2-yl)-2S-phenyl-ethyl]-amide (0.1mmol) in DCM (2 ml) is added over 15 min. The resulting reaction mixture is refluxed for 3.5 h and subsequently cooled down to 0 °C. Then aqueous ammonium chloride (1 ml) is added followed by EtOAc (5 ml). This solution is extracted with 0.1 N HCl (2 x 3 ml) and aqueous $NaHCO_3$ (2 x 3 ml). The organic layer is dried over sodium sulfate and the solvent evaporated. Flash-chomatography (silica gel, hexane/EtOAc) affords the desired product.

Example 25: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-(1-benzyl-2-hydroxy-4-phenylcarbamoyl-pentyl)]-amide

Mp: 191-196 °C
MS (LC/MS): 555 [M+Na]

Example 26: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-2-hydroxy-4-(pyridin-2-ylcarbamoyl)-pentyl]-amide

Mp: 126-130 °C
MS (ESI+): 534 [M+H]

Example 27: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-2-hydroxy-4-(pyridin-3-ylcarbamoyl)-pentyl]-amide

Mp: 186-194 °C
MS (LC/MS): 534 [M+H], 556 [M+Na]

Example 28: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-2-hydroxy-4-(pyridin-4-ylcarbamoyl)-pentyl]-amide

Mp: 197-200 °C
MS (LC/MS): 534 [M+H], 556 [M+Na]

Example 29: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-2-hydroxy-4-(isoxazol-3-ylcarbamoyl)-pentyl]-amide

Mp: 121-126 °C
MS (ESI+): 524 [M+H], 541 ($M+NH_4$)

Example 30: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-2-hydroxy-4-(5-methyl-1H-pyrazol-3-ylcarbamoyl)-pentyl]-amide

Mp: 172-176 °C
MS (LC/MS): 537 [M+H], 559 [M+Na]

Example 31: (S)-1-Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S,4R)-1-benzyl-2-hydroxy-4-(5-methyl-isoxazol-3-ylcarbamoyl)-pentyl]-amide

Rf: (DCM/methanol = 95/5): 0.45
MS (LC/MS): 560 [M+Na]

Example 32: (10R*)-10,11-Dihydro-dibenzo[b,f]oxepine-10-carboxylic acid [(1S*,2S*,4R*)-(1-benzyl-4-butylcarbamoyl-2-hydroxy-pentyl)-amide and (10S*)-10,11-Dihydro-dibenzo[b,f]oxepine-10-carboxylic acid [(1S*,2S*,4R*)-(1-benzyl-4-butylcarbamoyl-2-hydroxy-pentyl)-amide

These products are prepared from [(S*)-2-(phenyl)-1-((2S*,4R*)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester according to a procedure similar to steps 1f and 1g, using 10,11-dihydro-dibenz[b,f]oxepin-10-carboxylic acid and subsequent separation of the diastereoisomers (crystallization), followed by a protocol similar to step 1e.

(10R*)-Isomer: MS (LC/MS): 515 [M+H]
(10S*)-Isomer: MS (LC/MS): 515 [M+H]

Example 33: (S)-1-(5-Oxa-2-aza-dibenzo[a,d]cycloheptene-10-carboxylic acid) [(1S,2S,4R)-(1-benzyl-4-butylcarbamoyl-2-hydroxy-pentyl)]-amide

This product is prepared from [(S*)-2-(phenyl)-1-((2S*,4R*)-4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic acid tert-butyl ester and 5-Oxa-2-aza-dibenzo[a,d]cycloheptene-10-carboxylic acid according to a procedure similar to steps 1f, 1g and 1e of Example 1.

MS (LC/MS): 514 [M+Na]
Rf: (EtOAc/hexane = 1/1): 0.1

5-Oxa-2-aza-dibenzo[a,d]cycloheptene-10-carboxylic acid can be prepared as described hereafter:

a) 4-Phenoxy-nicotinic acid methyl ester

A suspension of 4-Chloro-nicotinic acid methyl ester (1.1 g), phenol (2.41 g, 4 eq.), potassium carbonate (3.55g, 4 eq.), copper (400 mg) and copper iodide (400 mg) in THF (35 ml) is stirred at 70 °C for 15 h. The mixture is cooled down to rt, diluted with water (20 ml) and extracted with diethyl ether (3 x 50 ml). Combined organic layers are dried over sodium sulfate and the solvent is evaporated. Resulting crude product was purified on silica (Flashmaster, EtOAc/hexane) to afford pure product (410 mg, 28 %).

MS (ESI+): 230 [M+H]
Rf: (EtOAc/hexane = 1/3): 0.2

b) (4-Phenoxy-pyridin-3-yl)-methanol

To a solution of 4-Phenoxy-nicotinic acid methyl ester (352 mg) in THF (4 ml) at 0 °C is added LAH (54 mg, 1 eq). After 5 min at 0 °C, 1 N aqueous sodium hydroxide (2 ml) is added and then the resulting solution is extracted with EtOAc (3 x 10 ml). Combined organic layers are washed with water (15 ml), dried over sodium sulfate and the solvent evaporated to provide pure product (270 mg, 94 %).

MS (ESI+): 202 [M+H]
Rf: (EtOAc/hexane = 2/1): 0.15

c) 4-Phenoxy-pyridine-3-carbaldehyde

To a solution of (4-Phenoxy-pyridin-3-yl)-methanol (270 mg) in DCM (10 ml) is added Dess-Martin periodinane (1.14 g, 2 eq.) and pyridine (2.16 ml, 20 eq.). After stirring the reaction mixture for 1 h at rt 10 % aqueous sodium bicarbonate solution (15 ml) is added and the solution is extracted with DCM (3 x 15 ml). Combined organic layers are dried over sodium sulfate, the solvent is evaporated and the crude product purified on silica (Flashmaster, EtOAc/hexane) to afford pure aldehyde (238 mg, 89 %).

MS (ESI+): 200 [M+H]

1H-NMR (400 MHz, CDCl3): delta = 10.65 (s, 1H); 9.05 (s, 1H); 8.58 (d, 1H); 7.58 (t, 2H); 7.49 (t, 1H); 7.21 (s, 1H); 6.98 (s, 1H); 6.70 (d, 1H).

d) 5-Oxa-2-aza-dibenzo[a,d]cycloheptene-10-carboxylic acid

A mixture of 4-Phenoxy-pyridine-3-carbaldehyde (50 mg), hippuric acid (45 mg, 1 eq.) and sodium acetate (25 mg, 1.2 eq.) in acetic anhydride (1 ml) is heated at 80 °C for 1 h before adding water (0.2 ml). After another h at 80 °C, the solution is cooled to rt and concentrated HCl (0.5 ml) and acetic acid (0.2 ml) are added. After 1 h at rt, concentrated sulfuric acid is added and the solution is stirred at 150 °C over night, cooled down to rt and poured into an ice-aqueous sodium hydroxide solution (5 ml) to adjust the pH to 6. This mixture is extracted with EtOAc (3 x 10 ml). Combined organic layers are dried over sodium sulfate, the solvent is evaporated and the crude product crystallized to afford pure 5-Oxa-2-aza-dibenzo[a,d]cycloheptene-10-carboxylic acid (35 mg, 58 %).

MS (ESI-): 238 [M-H]

MS (ESI+): 240 [M+H]

Example 34: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(3-methyl-benzylamino)-propyl]-amide

A solution of 526 mg tert.Butyl(S-(R,R)(-)-(1-oxiranyl-2-phenylethyl)-carbamate and 1.25 ml 3-Methylbenzylamine in 5 ml ethanol is heated for 3 h at 50°C. Evaporation of the solvent and purification by FC (DCM/methanol 9:1) yields 678 mg of [(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methyl-benzylamino)-propyl]-carbamic acid tert-butyl ester as a colorless solid. This material is suspended in 20 ml 4N HCl in dioxane an stirred for 20 h. The suspension is

filtered, the solid washed with DCM, dissolved in 10 ml 1 M sodium hydroxide and extracted twice with DCM. After drying with $MgSO_4$, the solvents are evaporated in vacuo and the crude material is used without further purification. A solution of 80 mg crude (2R,3S)-3-Amino-1-(3-methyl-benzylamino)-4-phenyl-butan-2-ol, 76 mg Dibenzo[b,f]oxepine-10-carboxylic acid, 106 mg TBTU and 185 µl NMM in 6 ml DCM is stirred 20 h at rt. The solution is diluted with with 40 ml DCM, washed with a solution sat. bicarbonate, sat. brine, 0.1 M HCl and finally with sat. bicarbonate. After drying with $MgSO_4$ and evaporation of the solvent the product was purified by FC (DCM/methanol 95:5) to yield 98 mg of Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(3-methyl-benzylamino)-propyl]-amide

MS (ESI+): 505 [M+]
Rf: 0.13 (DCM/methanol = 95/5)

Example 35: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2R)-1-benzyl-3-(3,3-diphenyl-propylamino)-2-hydroxy-propyl]-amide, salt with Trifluoroacetate

A mixture of 80 mg tert.Butyl(S-(R,R)(-)-(1-oxiranyl-2-phenylethyl)-carbamate and 72 mg 3,3-Diphenylpropylamine in 1 ml ethanol is stirred at 50°C for 12 h. The reaction mixture is evaporated, yielding 164 mg of raw product ([(1S,2R)-1-Benzyl-3-(3,3-diphenyl-propylamino)-2-hydroxy-propyl]-carbamic acid tert-butyl ester). This crude material is treated for 3 h with 0.8 ml of a 4 M solution of HCl in dioxan at rt. After evaporation to dryness, the raw material (193 mg) is stirred with 78 mg Dibenzo[b,f]oxepine-10-carboxylic acid, 173 mg HBTU and 0.2 ml Huenig base in 4 ml DCM for 12 h at rt. The reaction mixture is evaporated and purified by preparative HPLC (gradient of water, 0.1% TFA/ acetonitrile, 0.1% TFA from 80/20 to 0/100 on Nucleosil 100-10 C18 column). The fractions containing are lyophilized giving 130 mg of the trifluoroacetate salt of Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2R)-1-benzyl-3-(3,3-diphenyl-propylamino)-2-hydroxy-propyl]-amide

MS (ESI+): 595 [M+H]
Rf: 0.7 (DCM/methanol = 9/1, 1% NH_3)

The following compounds are synthesized according to the procedures given in Examples 34 or 35.

Example 36: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S)-1-benzyl-3-(benzyl-phenethyl-amino)-2-hydroxy-propyl]-amide

MS (ESI+): 595 [M+]
Rf: 0.1 (Hex/EtOAc = 4/1)

Example 37: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-3-[(furan-2-ylmethyl)-amino]-2-hydroxy-propyl}-amide

MS (ESI+): 482 [M+]
Rf: 0.42 (DCM/methanol = 9/1)

Example 38: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-amide

MS (ESI+): 521 [M+]
Rf: 0.06 (DCM/methanol = 95/5)

Example 39: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2R)-1-benzyl-3-(benzyl-phenethyl-amino)-2-hydroxy-propyl]-amide

MS (ESI+): 595 [M+]
Rf: 0.11 (DCM/methanol = 98/2)

Example 40: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S)-1-benzyl-2-hydroxy-3-(3-phenyl-propylamino)-propyl]-amide, salt with trifluoroacetate

MS (ESI+): 519 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.59

Example 41: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2S)-1-benzyl-3-[(biphenyl-3-ylmethyl)-amino]-2-hydroxy-propyl}-amide

MS (ESI+): 567 [M+]

Rf: 0.15 (DCM/methanol = 95/5)

Example 42: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S)-1-benzyl-2-hydroxy-3-(3-phenoxy-benzylamino)-propyl]-amide

MS (ESI+): 583 [M+]
Rf: 0.1 (DCM/methanol = 95/5)

Example 43: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S)-1-benzyl-2-hydroxy-3-(4-[1,2,3]thiadiazol-4-yl-benzylamino)-propyl]-amide

MS (ESI+): 575 [M+]
Rf: 0.07 (DCM/methanol = 95/5)

Example 44: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S)-1-benzyl-3-(1-benzyl-butylamino)-2-hydroxy-propyl]-amide, salt with trifluoroacetate

MS (ESI+): 547 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.81

Example 45: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S)-1-benzyl-2-hydroxy-3-(4-phenyl-butylamino)-propyl]-amide, salt with trifluoroacetate

MS (ESI+): 533 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.52

Example 46: Dibenzo[b,f]oxepine-10-carboxylic acid ((1S,2S)-1-benzyl-2-hydroxy-3-phenethylamino-propyl)-amide, salt with trifluoroacetate

MS(ESI+): 505 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.61

Example 47: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S)-1-benzyl-2-hydroxy-3-((R)-2-phenyl-propylamino)-propyl]-amide, salt with trifluoroacetate

MS (ESI+): 519 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.71

Example 48: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2S)-1-benzyl-2-hydroxy-3-(1-methyl-3-phenyl-propylamino)-propyl]-amide, salt with trifluoroacetate

MS (ESI+): 533 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.69

Example 49: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-2-hydroxy-3-[2-(2-hydroxy-ethyl)-benzylamino]-propyl}-amide

MS (ESI+): 535 [M+]
Rf: 0.4 (DCM/methanol = 90/10)

Example 50: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-2-hydroxy-3-[3-(3-methoxy-propoxy)-benzylamino]-propyl}-amide

MS (ESI+): 579 [M+]
Rf: 0.01 (DCM/methanol = 95/5)

Example 51: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-2-hydroxy-3-[methyl-((R)-1-phenyl-ethyl)-amino]-propyl}-amide

MS (ESI+): 519 [M+]
Rf: 0.53 (DCM/methanol = 90/10)

Example 52: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-((S)-1-phenyl-ethylamino)-propyl]-amide

MS (ESI+): 505 [M+]
Rf: 0.13 (DCM/methanol = 95/5)

Example 53: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-((S)-1-naphthalen-2-yl-ethylamino)-propyl]-amide

MS (ESI+): 555 [M+]
Rf: 0.18 (DCM/methanol = 90/10)

Example 54: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-2-hydroxy-3-[(S)-1-(3-methoxy-phenyl)-ethylamino]-propyl}-amide

MS (ESI+): 535 [M+]
Rf: 0.15 (DCM/methanol =95/5)

Example 55: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(2-pyridin-4-yl-ethylamino)-propyl]-amide

MS (ESI+): 506 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.12

Example 56: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-2-hydroxy-3-[2-(4-methoxy-phenyl)-ethylamino]-propyl}-amide, salt with trifluoroacetic acid

MS (ESI+): 535 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.49

Example 57: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-2-hydroxy-3-[2-(3-methoxy-phenyl)-ethylamino]-propyl}-amide, salt with trifluoroacetic acid

MS (ESI+): 535 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.51

Example 58: Dibenzo[b,f]oxepine-10-carboxylic acid ((1S,2R)-1-benzyl-3-cyclopropylamino-2-hydroxy-propyl)-amide, salt with trifluoroacetic acid

MS (ESI+): 441 [M+H]

Rf: (DCM/methanol = 9/1, 1% NH_3): 0.53

Example 59: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(2-pyridin-2-yl-ethylamino)-propyl]-amide

MS (ESI+): 506 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.17

Example 60: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2R)-1-benzyl-2-hydroxy-3-(2-pyridin-3-yl-ethylamino)-propyl]-amide

MS (ESI+): 506 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.12

Example 61: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-2-hydroxy-3-[(pyridin-3-ylmethyl)-amino]-propyl}-amide

MS (ESI+): 492 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.18

Example 62: Dibenzo[b,f]oxepine-10-carboxylic acid ((1S,2R)-1-benzyl-3-cyclohexylamino-2-hydroxy-propyl)-amide, salt with trifluoroacetic acid

MS (ESI+): 483 [M+H]
Rt HPLC (Nuc C-18HD, water/acetonitril/0.1 % TFA = 80/20 -> 0/100 in 6 min): 3.99 min

Example 63: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-3-[(1H-benzoimidazol-2-ylmethyl)-amino]-1-benzyl-2-hydroxy-propyl}-amide, salt with trifluoroacetic acid

MS (ESI+): 531 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.17

Example 64: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-2-hydroxy-3-[2-(2-methoxy-phenyl)-ethylamino]-propyl}-amide, salt with trifluoroacetic acid

MS (ESI+): 535 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.47

Example 65: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-2-hydroxy-3-[(pyridin-4-ylmethyl)-amino]-propyl}-amide

MS (ESI+): 492 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.21

Example 66: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-4-[bis-(4-ethyl-benzyl)-amino]-2-hydroxy-butyl}-amide

A solution of (2S,3R)-2-Amino-5-[bis-(4-ethyl-benzyl)-amino]-1-phenyl-pentan-3-ol (13 mg), salt with two trifluoroacetic acids, Dibenzo[b,f]oxepine-10-carboxylic acid (5 mg), HBTU (11 mg) and N-Ethyl-diisopropylamine (0.007 ml in 2 ml DCM) is stirred for 16 h at rt. The reaction mixture is evaporated and purified by flash chromatography with hexane/ EtOAc /NH3 = 3/1/0.01. 4.7 mg of desired product are obtained.

MS (ESI+): 651 [M+H]
Rf: (cyclohexane/ EtOAc /DIPEA = 2/1/0.01): 0.30

The starting materials can be prepared as described hereafter:

a) ((1S,2R)-1-Benzyl-3-cyano-2-hydroxy-propyl)-carbamic acid tert-butyl ester
To a solution of tert.Butyl(S-(R,R)(-)-(1-oxiranyl-2-phenylethyl)-carbamate (1.0 g) in THF (2.2 ml), 2-hydroxy-2-methylpropanenitrile (0.4 ml) and triethyl amine (0.6 ml) is added. The mixture is stirred for 16 h under reflux. After evaporation the remaining material is taken up in EtOAc and extracted with brine. The organic layer is dried over sodium sulfate and the solvent evaporated under reduced pressure to afford ((1S,2R)-1-Benzyl-3-cyano-2-hydroxy-propyl)-carbamic acid tert-butyl ester (1.1 g).

MS (ESI+): 234 [M - tert-Butyl]

b) ((1S,2R)-4-Amino-1-benzyl-2-hydroxy-butyl)-carbamic acid tert-butyl ester

To a suspension of LAH (0.6 g) in THF (40 ml) is adeed at 0 °C a solution of ((1S,2R)-1-Benzyl-3-cyano-2-hydroxy-propyl)-carbamic acid tert-butyl ester (1.1 g) in THF (15 ml). The mixture is stirred for 1 h at 0 °C and then quenched with water and 3N aqueous sodium hydroxide. After filtration the solution is concentrated under reduced pressure and purified by preparative HPLC (gradient of water, 0.1% TFA/ acetonitrile, 0.1% TFA from 80/20 to 0/100 on Nucleosil 100-10 C18 column). The fractions containing ((1S,2R)-4-Amino-1-benzyl-2-hydroxy-butyl)-carbamic acid tert-butyl ester are set to a basic pH by addition of soda and extracted with EtOAc. The organic layer is dried over sodium sulfate and concentrated under reduced pressure to give 682 mg of the desired product.
MS (ESI+): 295 [M+H]

c) (2S,3R)-2-Amino-5-(4-ethyl-benzylamino)-1-phenyl-pentan-3-ol, salt with two trifluoroacetic acids and (2S,3R)-2-Amino-5-[bis-(4-ethyl-benzyl)-amino]-1-phenyl-pentan-3-ol, salt with two trifluoroacetic acids

A solution of ((1S,2R)-4-Amino-1-benzyl-2-hydroxy-butyl)-carbamic acid tert-butyl ester (80 mg) and 4-ethyl-benzaldehyde (0.037 ml) in ethanol/acidic acid (2.2 ml, 10/1) is stirred for 1.5 h at rt. The reaction mixture is cooled to 0 °C and sodium cyanoborhydride (13 mg) is added. After further 1.5 h at rt, the reaction mixture is evaporated and the remaining solid taken up in EtOAc and extractet with 10% soda and brine. The organic layer is dried over sodium sulfate and concentrated to afford crude product (105 mg). Without further purification the crude material is stirred at rt in 4N HCl /dioxane (2 ml) for 1 h. The reaction mixture is concentrated and purified by preparative HPLC (gradient of water, 0.1% TFA/ acetonitrile, 0.1% TFA from 80/20 to 0/100 on Nucleosil 100-10 C18 column). The fractions containing the desired products are lyophilized. Two products are isolated: (2S,3R)-2-Amino-5-(4-ethyl-benzylamino)-1-phenyl-pentan-3-ol, salt with two trifluoroacetic acids: 92 mg, MS (ESI+): 313 [M+H]
and (2S,3R)-2-Amino-5-[bis-(4-ethyl-benzyl)-amino]-1-phenyl-pentan-3-ol, salt with two trifluoroacetic acids: 13 mg, MS (ESI+): 431 [M+H]

The following compounds are synthesized according to the procedures given in Example 66.

Example 67: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-4-[bis-(4-methoxy-benzyl)-amino]-2-hydroxy-butyl}-amide

MS (ESI+): 655 [M+H]
Rf: (cyclohexane/ EtOAc /DIPEA = 1/1/0.01): 0.40

Example 68: Dibenzo[b,f]oxepine-10-carboxylic acid {(1S,2R)-1-benzyl-4-[bis-(3-methoxy-benzyl)-amino]-2-hydroxy-butyl}-amide

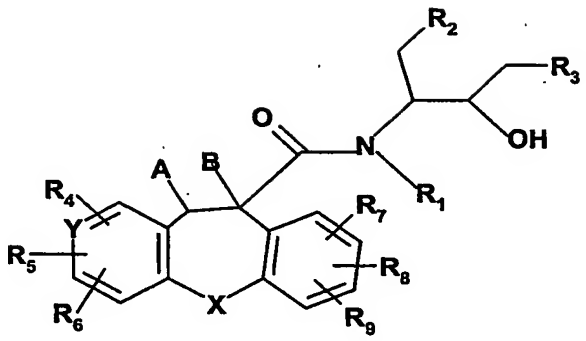
MS (ESI+): 655 [M+H]
Rf: (cyclohexane/ EtOAc /DIPEA = 1/1/0.01): 0.59

Example 69: Dibenzo[b,f]oxepine-10-carboxylic acid [(1S,2R)-1-benzyl-4-(4-ethyl-benzylamino)-2-hydroxy-butyl]-amide

MS (ESI+): 533 [M+H]
Rf: (DCM/methanol = 9/1, 1% NH_3): 0.43

Claims:

1. A compound of formula I



I

wherein

X is O, NH, N(C_{1-4})alkyl, CO or CHOH,

Y is CH or N,

A and B are each hydrogen or together form a second bond between the carbon atoms to which they are attached,

R_1 is hydrogen or (C_{1-4})alkyl,

R_2 is optionally substituted (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl or heteroaryl,

R_3 is $CH(R_e)CONR_aR_b$ or $(CH_2)_nNR_cR_d$,

n is 0, 1 or 2,

R_a, R_b, R_c and R_d, independently, are hydrogen or optionally substituted (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl, aryl(C_{1-4})alkyl, heteroaryl or heteroaryl(C_{1-4})alkyl or

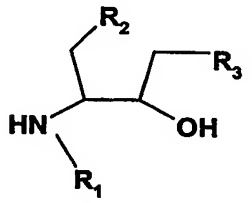
R_a, R_b, R_c and R_d, together with the nitrogen to which they are attached, form an optionally substituted pyrrolidinyl, piperidino, morpholino or piperazinyl group,

R_e is (C_{1-8})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{3-7})cycloalkyl or (C_{3-7})cycloalkyl(C_{1-4})alkyl, and

R_4, R_5, R_6, R_7, R_8 and R_9, independently, are hydrogen, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})alkyl-SO_2, cyano, nitro or halogen,

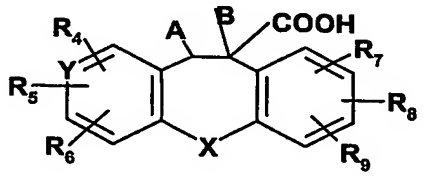
in free base or acid addition salt form.

2. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, which includes the steps of acylating a compound of formula II



II

wherein R_1, R_2 and R_3 are as defined in claim 1, with an acid of formula III



III

wherein X, Y, A, B, R_4, R_5, R_6, R_7, R_8 and R_9 are as defined in claim 1, or an activated form thereof, and recovering the so obtained compound of formula I in free base or acid addition salt form.

3. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

4. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

5. A pharmaceutical composition comprising a compound of claim 1 in free base of pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

6. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical, for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

7. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

8. A method for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form.

9. A combination comprising a therapeutically effective amount of a compound of claim 1 in free base of pharmaceutically acceptable acid addition salt form and a second drug substance, for simultaneous or sequential administration.